

REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 1-11 are currently pending and under examination in the application. Without acquiescence to the rejection and without prejudice to pursuing the encompassed subject matter in a related divisional, continuation, or continuation-in-part application, claim 2 is hereby canceled and claim 4 has been amended to maintain proper dependency.

INTERVIEW SUMMARY

Applicants kindly thank Examiner Tung for sharing her time with Applicants' representatives in a telephonic interview on October 10, 2008. During this interview, Applicants' representatives clarified with the Examiner the inventive features of the presently claimed subject matter, particularly in view of the lack of expectation in the art at the time of filing with regard to successfully performing bisulfite reactions on nucleic acid bound to a solid phase, as evidenced by the previously submitted Declaration of Dr. Markert-Hahn. A copy of slides submitted to the Examiner in advance of the telephonic interview is attached.

REJECTIONS UNDER 35 U.S.C. § 103

A. The Examiner rejected claims 1-5 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* (U.S. Patent No. 5,786,146). The Examiner agrees at page 3 of the Action that Herman *et al.* do not disclose a nucleic acid that is bound to a solid phase and then deaminated. The Examiner asserts, however, that performing a deamination reaction on solid phase, as presently claimed, represents a mere re-ordering of the steps of Herman *et al.* to produce the same product.

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of non-obviousness over Herman *et al.* In particular, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) ([T]he USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the combined references teach or suggest all the claim features, and even

assuming, *arguendo*, that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). Here, Herman *et al.* (1) fail to teach or in any way suggest the active step recited in claim 1(b) of “incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated,”; and (2) further fail to provide the requisite motivation and reasonable expectation of success to perform such a step.

With respect to the first point noted above, Applicants submit that it is clear that Herman *et al.* fail to teach or suggest each feature of the instant claims. Specifically, as acknowledged by the Examiner at page 3 of the Action, Herman *et al.* fail to teach or even remotely suggest the active, recited step of performing a deamination reaction on solid phase, such as by “incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated.” To the contrary, Herman *et al.*, at best, perform deamination reactions in solution (see, e.g., column 11, lines 15-28 of Herman *et al.*). In failing to teach or suggest each active, recited step of the instant claims, Herman *et al.* absolutely fail to establish the minimum elements of a *prima facie* case of obviousness over the presently claimed subject matter.

Applicants further submit that it is not at all surprising that Herman *et al.* fail to teach or suggest the recited step of performing a deamination reaction on solid phase, because a person skilled in the art at the time of filing would have expected such a reaction to produce no useful results whatsoever. Indeed, at the time of filing, bisulfite ions were believed to interact only with cytosines that do not participate in base-pairing (see Items 5 and 12 of the Declaration of Dr. Markert-Hahn, submitted with the Amendment/Response filed April 15, 2008). In fact, single-stranded DNA was believed to interact with a solid phase as if it were participating in base-pairing (see *Id.*). Thus, bisulfite ions were not expected to be able to physically interact with the cytosines in single-stranded DNA bound to a solid phase (see *Id.*). Since bisulfite ions must physically interact with the cytosines in DNA to achieve deamination, a person skilled in

the art at the time of filing would have expected a bisulfite reaction performed on solid phase, as recited in claim 1(b), to produce no useful results whatsoever. Accordingly, Herman *et al.*, or any other reference from the time of filing, would have no reason to recite the active, recited step of the present claims of incubating the solid phase bound nucleic acid in the presence of sulfite ions, whereby the nucleic acid is deaminated.

Applicants also submit that the instant claims clearly represent more than a mere re-ordering of steps to produce the same product of Herman *et al.*, as asserted by the Examiner at page 3 of the Action. Rather, the steps of the presently claimed method are fundamentally different than the steps performed by Herman *et al.*, since the presently claimed method requires deamination of solid phase bound nucleic acid, while Herman *et al.* describe deamination of nucleic acid in solution. Furthermore, Applicants note that by performing different steps (*i.e.*, sulfite reactions on solid phase), and by producing any result at all (*see, e.g.*, paragraph [0159] of the published application), these claims represent an unexpected and surprising discovery at the time of filing. In this manner, the instant facts are clearly distinguishable from the facts in the cases cited by the Examiner at page 3 of the Action (*see Ex parte Rubin*, 128 U.S.P.Q. 440 (Bd. App. 1959); *In re Burkhangs*, 154 F.2d 690 (CCPA 1946); and *In re Gibson*, 39 F.2d 975 (CCPA 1930)), since none of the Applicants in these cases provided evidence that the results obtained from the claimed processes were unexpected or surprising. The surprising and unexpected nature of the discovery that deamination reactions could be performed on nucleic acid bound to a solid phase clearly supports the non-obviousness of the instant claims.

Addressing the second point noted above, Applicants further submit that the Examiner has failed to establish that the skilled artisan would have the requisite motivation to produce the claimed method and any reasonable expectation of success in doing so. Contrary to the expectations at the time of filing, the instant application demonstrates successful bisulfite reactions performed on solid phase bound nucleic acid (*see* Example 5). Applicant submits that Herman *et al.* fail to teach or in any way suggest the active, recited step performing a deamination reaction on solid phase, such as by incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated. Moreover, in view of the understanding in the art at the time of filing, as evidenced by the Declaration of Dr. Markert-

Hahn and discussed above, a person skilled in the art at that time would have had no motivation to perform such a step with any expectation of success, let alone the requisite reasonable expectation of success. Since the requisite elements of a *prima facie* case of obviousness are missing, Applicants submit that the Herman *et al.* fail to establish a *prima facie* case of obviousness over the presently claimed subject matter.

Moreover, Applicants submit that the present invention provides surprising and unexpected results that further support the non-obviousness of the presently claimed methods. As previously made of record, the unexpected and surprising discovery that bisulfite reactions could be performed on solid phase bound nucleic acid provides distinct, technical advantages over the solution-based reactions of Herman *et al.*. For instance, the solution-based bisulfite reactions of Herman *et al.* are “cumbersome, time consuming and hardly applicable to routine diagnostics, let alone suitable for automation” (see Item 6 of the Declaration of Dr. Markert-Hahn). In contrast to Herman *et al.*, the use of solid-phase during deamination and desulfonation allows easier handling that is amenable to automation, among other advantages apparent to a person skilled in the art (see, e.g., paragraph [0011] of published U.S. Application No. 10/647,720).

In view of the above remarks, Applicants submit that the instant claims satisfy the requirements of obviousness over Herman *et al.*, and respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

B. The Examiner rejected claims 6-11 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.*, as applied to claims 1-5 in section A above, in view of Weindel *et al.* (WO 2001/37291). The Examiner agrees that Herman *et al.* fail to disclose the use of magnetic glass particles as a solid phase, but asserts that Weindel *et al.* disclose the use of magnetic glass particles for nucleic acid purification. The Examiner then asserts that it would have been obvious to use the the magnetic glass particles in the method of Herman *et al.*

Applicants traverse this rejection and submit that the instant claims satisfy the requirements of non-obviousness. In particular, Applicant submits that neither Herman *et al.* nor Weindel *et al.*, alone or in combination, teach or suggest each feature of the instant claims.

As detailed in section A above, Herman *et al.* fail to teach or in any way suggest the active, recited step of incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated, as recited in independent claim 1, from which the instant claims depend. Weindel *et al.* do not remedy this deficiency, as this reference is similarly silent with respect to performing deamination reactions on solid phase bound nucleic acid. In failing to teach or suggest each feature of the instant claims, the cited references in combination fail to establish the minimum requirements of a *prima facie* case of obviousness.

Moreover, Applicant submits that even if a person skilled in the art at the time of filing combined the methods of Herman *et al.* and Weindel *et al.*, as proposed by the Examiner at page 4, last paragraph, of the Action, such a person would not arrive at the presently claimed subject matter. To the contrary, the combination proposed by the Examiner does not teach a person skilled in the art to perform the deamination reactions on solid phase, as recited in independent claim 1, but instead teaches that person to perform such reactions in solution. Thus, a person skilled in the art at the time of filing would have had to embark on a whole new line of experimentation to arrive at the presently claimed method, which would have required that person to go against the expectations in the art at the time of filing, as discussed in section A above (*see, e.g.*, Items 5 and 12 of the Declaration of Dr. Markert-Hahn).

Given the deficiencies in both Herman *et al.* and Weindel *et al.*, Applicants submit that these references, alone or in combination, fail to render the instant claims obvious. Applicants submit that the instant claims satisfy the requirements of non-obviousness, and respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Applicants submit that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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USSN 10/647,720

Determining Methylation Positions in a Nucleic Acid

- Pending claims are directed to a method of bisulfite treatment (deamination and desulfonation steps) of nucleic bound to a solid phase to convert cytosines to uracils, by performing, in part, the following steps:
 - **Binding nucleic acid to a solid phase**
 - **Incubating solid phase bound nucleic acid in the presence of sulfite ions (deamination step)**
 - **Incubating solid phase bound nucleic acid under alkaline conditions (desulfonation step)**
- Examples demonstrate successful bisulfite reactions performed on solid phase bound nucleic acid
 - **(see Examples 2-5)**

Hermann (US 5,786,146)

- The bisulfite reactions of Hermann are performed on nucleic acid in solution.
 - **See column 11, lines 15-28, Example 1.**
 - **Herman describes no further bisulfite reactions**
- Thus, distinct from the instant claims, the bisulfite sulfite reactions of Hermann are NOT performed on nucleic acid bound to a solid phase
- The cited prior art does not teach each step of the method of claim 1 and, thus, cannot render claim 1 obvious.

Hermann (US 5,786,146)

- The Examiner's assertions:
 - Hermann suggests that after the bisulfite reaction, and after amplification of the nucleic acid sequences, these amplified sequences can be bound to solid support for further evaluation
 - The Examiner, thus, asserts that by first binding nucleic acid to a solid phase, the instant claims represent a mere re-ordering of the steps of Hermann to produce the same product

No Reasonable Expectation of Success for Solid-Phase Bisulfite Reactions

- At the time of filing, the Examiner's alleged re-ordering of the steps of Hermann by first binding the nucleic acid to a solid phase, followed by performing a bisulfite reaction, would not have been expected to produce any results at all

No Reasonable Expectation of Success for Solid-Phase Bisulfite Reactions

- The state of the art at the time of filing considered that bisulfite reactions could not be performed on solid phase bound single-stranded DNA.
 - **Bisulfite ions were believed to interact only with cytosines that do not participate in base-pairing**
 - **Single-stranded DNA was believed to interact with solid phase as if it were participating in base-pairing.**
 - **Thus, bisulfite ions were not expected to be able to physically interact with single-stranded DNA bound to a solid phase**
- (see Markert-Hahn Declaration, Items 5 & 9)

No Reasonable Expectation of Success for Solid-Phase Bisulfite Reactions

- Contrary to the expectations in the art at the time of filing, the instant application demonstrates successful bisulfite reactions performed on solid phase bound nucleic acid (*see* Examples 2-5)
- Thus, the instant claims represent more than a mere re-ordering of steps to produce the same product of Hermann, but by
 - performing different steps (reactions on solid phase), and
 - producing any result at all,
- these claims represent an unexpected and surprising discovery at the time of filing

Advantages Over Hermann

- The solution-based bisulfite reactions of Hermann are “cumbersome, time consuming and hardly applicable to routine diagnostics, let alone suitable for automation.”
 - See Markert-Hahn Declaration, Item 6.
- In contrast to Hermann, the use of solid-phase during deamination and/or desulfonation allows easier handling that is amenable to automation.
 - See paragraph [0011] of published USSN 10/647,720

Performing Different Steps

Instant Claims

Hermann

Bind DNA to solid phase

DNA in solution



Deaminate **while bound**

Deaminate in solution



Desulfonate **while bound**

Desulfonate in solution



Performing Different Steps That Would Not Have Been Expected To Work At All

Instant Claims

Hermann

*Deaminate **while bound****

Deaminate in solution



Desulfonate **while bound**

Desulfonate in solution

* Bisulfite ions were not expected to be able to physically interact with single-stranded DNA bound to a solid phase.